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# Discriminative Effects of Morphine in the Pigeon[1]

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JÄRBE, TORBJÖRN U.C. *Discriminative effects of morphine in the pigeon.* PHARMAC. BIOCHEM. BEHAV. 9(4) 411–416, 1978.—Pigeons were trained to discriminate between the effects of morphine (6 mg/kg) and saline injected IM, 45 min prior to training in a box equipped with 2 response keys which were mounted left and right on the front panel. Reinforcement (food) was contingent upon pecking (FR 15) on one key when trained under the influence of morphine (6 mg/kg) and the other key when trained with saline. After the choice of key (left or right) had become conditioned to the presence or absence of the effects of morphine, test sessions under new drug conditions were interspersed between the regular training sessions. The median effective dose of morphine and the time interval since the morphine injection in producing 50% morphine appropriate responding by the pigeons were respectively: 1.6 mg/kg and 6 hr post-injection. A stereoisomeric requirement for the discrimination was evident because treatment with levorphanol (2 mg/kg) resulted in responding on the morphine appropriate key while treatments with the enantiomer dextrorphan (1–10 mg/kg) predominantly yielded responding on the saline appropriate key. In addition, methadone (3 and 6 mg/kg) substituted for morphine while tests with 3 other psychotropic drugs $\Delta^9$-THC (0.25 and 0.50 mg/kg), d-LSD (0.04 and 0.08 mg/kg) and pentobarbital (4 and 8 mg/kg)) resulted in responding appropriate for the saline-induced training condition. The opioid antagonists naloxone and naltrexone blocked the stimulus effects of morphine (6 mg/kg). Naloxone appeared less potent in this respect than its congener, naltrexone, when the drugs were evaluated 45 min post-injection. Thus the discriminable effects of morphine in the pigeon are qualitatively similar to the results obtained in mammals (gerbils, rats, and squirrel monkeys) required to discriminate morphine from a nondrug condition.

Drug discrimination Morphine Transfer Antagonism Pigeons

ONE OF THE more extensively studied groups of drugs with respect to the ability to serve as a discriminative stimulus in rats has been narcotic analgesics such as morphine [2, 11, 12, 13, 19, 23, 25, 26, 27, 29, 30] and fentanyl [3]. Taken together, the studies strongly suggest that these discriminations meet several generally accepted criteria to classify them as being of a specific narcotic nature in that (a) narcotic analgesics with predominant agonistic activity can substitute for each other's discriminable effects; (b) the discriminable effects of narcotics are blocked by antagonists such as naloxone and naltrexone; (c) a structural, stereoisomeric requirement is needed to produce the narcotic discriminative-stimulus complex (DSC); (d) non-opioid drugs do not substitute for the discriminable effects of narcotic analgesics [3,15]. Whether or not discriminative effects of narcotic analgesics are subject to development of tolerance are, however, still debated [4, 12, 19, 25]. Although the rat has been the single most commonly used species for this kind of research, recent investigations suggest that some of the aforementioned criteria for the specificity of the narcotic DSC also apply to other mammalian species such as the gerbil [18] and the squirrel monkey [24].

The properties of morphine and related analgesic agonists that enable them to serve a discriminative function thereby guiding the choice behavior of animals appear at least superficially to be similar [3, 25, 26, 27] to those used by drug-experienced humans to indicate differences between narcotics vis-a-vis other psychotropic agents [10,21]. The drug discrimination paradigm might therefore be a useful model to study the subjective response characteristics to drugs in laboratory animals [1] and enables us to compare such effects across various species.

In the present study pigeons were trained to discriminate between the potentially discriminable effects induced by IM injections of morphine and those of saline in a food reward, two-choice discrimination paradigm in order to ascertain whether or not the above listed requirements for the narcotic DSC are applicable also to a non-mammalian species such as the pigeon.

## METHOD

### *Animals*

The subjects were 4 experimentally naive, mature male pigeons of a mixed strain (Estuna AB, Sweden). The free-feeding weight of the birds ranged between 316–358, averaging 339 g. Between experimental sessions the birds were

[1]A portion of the results was presented at the "Fifth Scandinavian Meeting on Physiology and Behavior", May 20–22, 1977, Helsinki, Finland.

maintained individually in a larger colony room (light from 800–2000 hr; temp. 20–22°C; relative humidity 50–55%. Water was continuously available and whenever necessary extra grain was supplied after the sessions to maintain the body weights of the pigeons at about 80% of their free-feeding weights.

*Apparatus*

The experimental chamber was similar to that described earlier [9,16]. The box was sound-attenuated and ventilated. The response keys, 2 cm in diameter and dimly illuminated with white light, were mounted horizontally 10 cm apart on the front panel in the chamber, each about 19 cm above the chamber floor. The minimum force necessary to operate the keys was about 15 g. The food-magazine was located in between the response keys, 4 cm above the floor of the chamber.

A reinforcement consisted of a 3-sec access to grain. The key light and house light went off simultaneously with the 3-sec operation of the grain magazine and illumination of the food by the magazine light. Conventional relay programming and recording apparatus were employed; these units were located in a room adjacent to that of the experimental chamber.

*Procedure*

*Discrimination training and testing.* The birds were trained to peck the center key to obtain food grains according to a FR 1 schedule; the requirements for obtaining food were then gradually increased until a FR 15 schedule was in operation, i.e., the birds had to peck the key 15 times in order to get access to food. When morphine was injected prior to a session the center key had been removed and only the key (left or right) appropriate for a given training condition (drug=D or no drug=N) was available. Sessions were forced during 22 sessions before the free-choice discrimination training began at which time both response keys were available. The animals now had to respond selectively on the appropriate key which depended upon whether morphine or saline had been administered in order to be reinforced with food; responses on the inappropriate key had no programmed consequences. Discrimination training followed a single alternation design (D, N, D, N, D, etc.) and the birds were trained 3 times per week (Mondays, Wednesdays and Fridays) for 10 min per session on a FR 15 schedule of reinforcement. The drug training condition (D) consisted of an injection of 6 mg/kg of morphine NCl and the no drug training (N) condition was 1 ml/kg of saline (0.9%) and the solutions were given IM 45 min prior to the sessions.

When the pigeons, depending upon the treatment (D or N), exhibited a correct key selection (left and right) at the onset of each training session during 8 out of 10 consecutive training days, the animals were switched to the test procedure. The sequence for training under morphine (6 mg/kg) or saline (1 mg/kg) on Mondays and Wednesdays and testing (T) on Fridays became D, N, T (Week 1), N, D, T (Week 2), D, N, T (Week 3), etc. The order of tests, except those given in Fig. 3B (see below), were randomized with the restriction that half the number of observations for each datum point were preceded by a D-training session and hence the remaining tests were preceded by a N-training session. The graph illustrating the interaction between the antagonists and morphine at the constant injection-test interval of 45 min (Fig. 3B) was obtained by testing progressively lower amounts of the antagonists, each dose-step being separated by 2 weeks, until a dose-level was found where all pecking responses were on the morphine associated key. During all of these tests the pigeons were allowed to perform 10 responses after which the program was switched off and the bird was returned to its home cage. During the last test, the pigeons could perform 225 responses during the 10 min period allowed and if all responses were on the selected key, i.e., the key on which the animal first achieved 15 responses, a total of 15 reinforcements would have been available. Pecking on the other, non-selected key did not activate the food-magazine.

*Data analysis.* Data are presented as the average percentage of pecking-responses on the morphine associated key (morphine key). A test drug was considered to substitute for the training dose of morphine if a mean of at least 80% of the responses by the group were on the morphine appropriate key. Also in the legends, the percentage of morphine appropriate responses are given for the initial 15, 45 and the total number of morphine appropriate choices emitted by the birds during all training sessions. The median effective dose (ED50) of morphine and time-interval (ET50) since injection of morphine in yielding 50% morphine responding were calculated according to the method by Litchfield and Wilcoxon [20]. Rates of responding were compared across sessions using the A-test for paired or matched contrasts [22].

*Drugs.* Morphine HCl and ampuls of 10 mg/ml of methadone HCl (ACO), naloxone HCl* and naltrexone HCl* (Endo), dextrorphan tartrate* and levorphanol tartrate* (Hoffman LaRoche), $\Delta^9$-tetrahydrocannabinol*, ($\Delta^9$-THC) (U.N. Narcotics Lab. at Geneva), d-lysergic acid diethylamide* (d-LSD) (Sandoz), and ampuls of pentobarbital sodium (50 mg/ml, Abbott) were used. All drugs except $\Delta^9$-THC were dissolved or diluted with saline (0.9%). Stock solutions of morphine and d-LSD were not older than 24 hr and the other drugs were dissolved, diluted or suspended shortly prior to use. The suspension of $\Delta^9$-THC was made in 10% propylene glycol, 1% polysorbate-80, and 89% normal saline according to the formula described by Sofia *et al.* [28] and used by us previously for IM injections in pigeons [9,16]. Doses refer to the forms indicated and all injections were IM (1 mg/kg). When 2 drugs (1 ml/kg for each drug formula) were given before a test session the drugs were injected in opposite sides of the breast muscle of the pigeons.

## RESULTS

*Acquisition of the Morphine Discrimination*

Figure 1 shows that the morphine (6 mg/kg) discrimination was rapidly established when both response keys (left and right) were available concurrently (free choice discrimination) to the birds. All 4 pigeons performed at least a mean of 90% correct responding during the initial 15 or 45 pecking-responses during 8 out of 10 training sessions (5 training sessions under each training condition).

The average number of responses per session was lower ($p<0.05$) for 3 of the birds during the morphine-drugged as compared to the nondrug training sessions. The response output for the fourth pigeon (P 35) was initially the same ($p>0.05$) during both training conditions. The lower response output under morphine sessions persisted during the entire test period for the former birds although the difference between the training sessions diminished for P 34. On the other hand, the response output for P 35 during morphine sessions became elevated ($p<0.001$). Thus, over continued

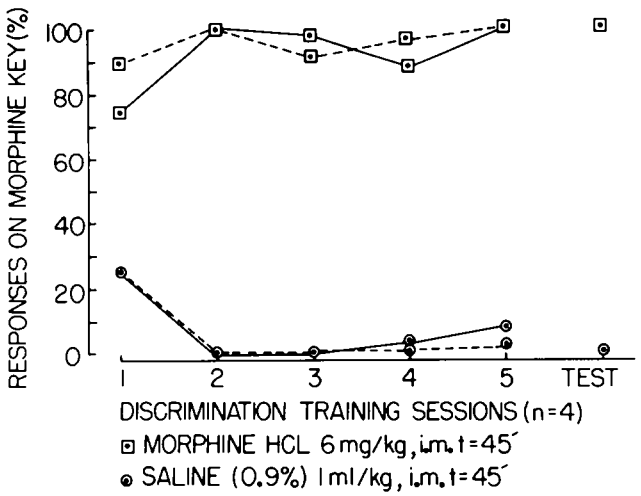


FIG. 1. Morphine discrimination in pigeons. The discriminative performance in terms of the percentage responses on the morphine associated key for the initial 15 (straight line) and 45 (dashed line) peckings for 4 pigeons required to discriminate between saline and 6 mg/kg of morphine. The number of animals for each datum point equals n=4. Tests are based on 10 pecking responses for each bird.

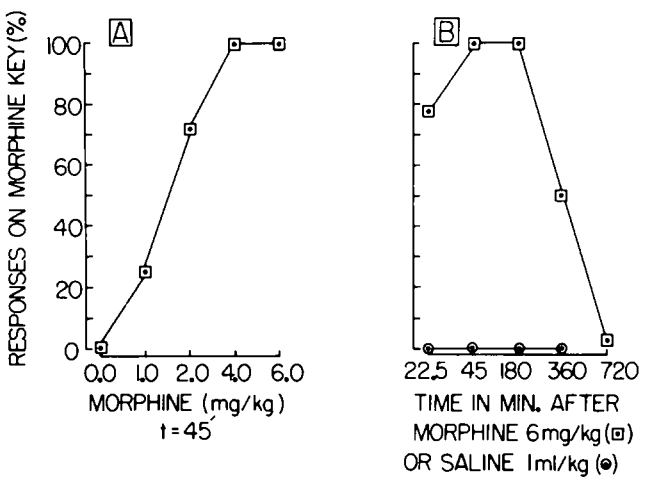


FIG. 2. Dose-response (A) and time-course (B) curves. Pigeons were trained to discriminate between saline (N) and 6 mg/kg of morphine (D). The regular injection-training interval was 45 min. The number of animals per datum point equals n=4, each bird performing 10 pecking-responses. The percentage responses to the morphine associated key for the initial 15, 45, and the total number of pecking responses during the drugged (D) and nondrugged (N) training sessions were respectively: D: 95.6, 95.8, 99.9% and N: 2.1, 0.1, 0.1% (A); D: 91.7, 93.6, 99.7%, and N: 0.0, 0.0, 0.6% (B).

training during the test phase, the response output of the decreased responding birds recovered slightly whereas 1 bird (P 35) exhibited an increase in responding on morphine days.

*Dose Generalization and Time Course of the Discriminable Effects of Morphine*

Figure 2 shows the effects of testing various doses of morphine injected IM, 45 min prior to testing (A) and the effects of testing a constant dose of morphine (6 mg/kg) at different time intervals after the IM injections of the drug (B). The ED50 and ET50 and the corresponding 95% confidence limits were respectively 1.6 (0.9–2.8) mg/kg and 360 (225–576) min post-injection. Regardless of the time-interval tested the vehicle (saline 1 ml/kg) induced only a selection of the saline appropriate response key. Thus the morphine-discrimination was both dose- and time-dependent.

*Stereoisomeric Specificity: Levorphanol and Dextrorphan*

In Fig. 3 it is illustrated that the levorotatory optical isomer levorphanol substituted for morphine while the analgesically inactive enantiomer, dextrorphan, was devoid of such a substitution effect. It should be added that 10 mg/kg of dextrorphan probably approximates the highest dose that can be tested in this situation because the latency to initiate responding was delayed several min in all the birds. At this dose the birds appeared to have difficulties in maintaining an upright position and in performing the key-pecking response. Also note that the potency of levorphanol is much greater than that of morphine. Thus levorphanol induces discriminable effects similar to morphine while dextrorphan does not.

*Antagonism of the Discriminable Effects of Morphine by Naloxone and Naltrexone*

Figure 4 shows the effects of testing the narcotic antagonists naloxone or naltrexone together with 6 mg/kg of morphine. Frame A of this figure suggests that both an-

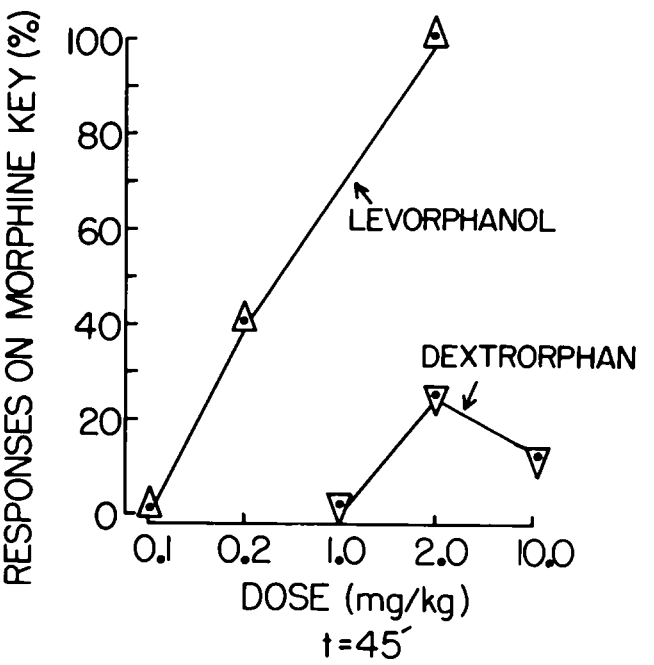


FIG. 3. Tests for stereospecificity by levorphanol and dextrorphan. Pigeons were trained to discriminate between saline (N) and 6 mg/kg of morphine (D). The number of animals per datum point equals n=4, each bird performing 10 pecking-responses. The percentage of responses on the morphine associated key for the initial, 15, 45, and the total number of pecking responses during the drugged (D) and nondrugged (N) training sessions were respectively: D: 92.5, 96.1, 99.5% and N: 0.3, 0.1, 0.2%.

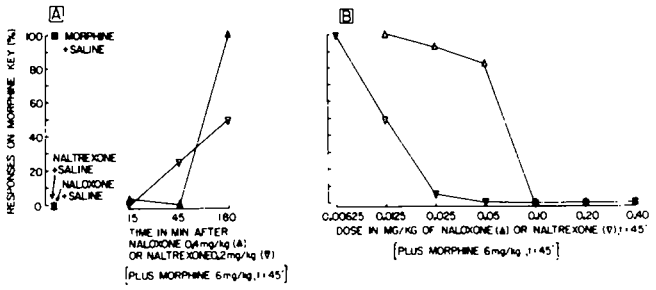


FIG. 4. Antagonism of the cue effects of morphine. Dose response curves for the antagonism of morphine (6 mg/kg) by naloxone and naltrexone when given at varous time intervals (A) and when given at a constant interval (B) prior to testing. The pigeons were trained to discriminate between saline (N) and 6 mg/kg of morphine (D). The number of animals per datum point equals n = 4, each bird performing 10 pecking-responses. In frame A, tests with combinations of saline (1 ml/kg, $t = 45'$) and naloxone (0.4 mg/kg, $t = 15'$) or naltrexone (0.2 mg/kg, $t = 15'$) as well as morphine (6 mg/kg, $t = 45'$) and saline (1 mg/kg, $t = 15'$) are also shown. The percentage responses on the morphine-associated key for the initial 15, 45 and the total number of pecking responses during the drugged (D) and nondrugged (N) training sessions were respectively: D: 96.5, 98.5, 99.3%, and N: 1.7, 0.6, 0.4% (A); D: 97.0, 97.3, 99.4%, and N: 0.2, 0.1, 0.2% (B).

tagonists are able to antagonize morphine-key responding when given only 15 min prior to testing. Morphine-key responding is reduced also 45 min after the narcotic antagonists, whereas tests conducted 3 hr after the narcotic antagonists suggest a shorter duration of action of naloxone (or a lower intrinsic antagonistic potency) than that for naltrexone in blocking the discriminable effects of morphine. Figure 4B shows that the morphine blocking efficacy of naltrexone (ED50≈0.0125 mg/kg) is 4–6 times greater than that of naloxone (ED50≈0.5–0.7 mg/kg) when both antagonists were evaluated 45 min post-injection. Neither of the 2 antagonists affected the saline-induced performance nor did an additional injection of saline (1 ml/kg) affect the morphine performance. Thus both naloxone and naltrexone block the discriminable effects of morphine, an effect that appears both time- and dose-related.

### *Narcotic Specificity: Methadone and Non-Opioid Psychopharmacologic Drugs*

Table 1 shows that substitution tests with methadone (3 and 6 mg/kg) resulted in morphine-key responding, i.e., the birds predominantly selected the morphine associated key. Tests with 3 other psychotropic drugs ($\Delta^9$-THC, d-LSD and pentobarbital) resulted in a key selection appropriate for the nondrug training condition. Thus the effects of the latter 3 drugs were not perceived as similar to the morphine-induced condition.

## DISCUSSION

The present study has shown that 6 mg/kg of morphine injected IM 45 min prior to sessions is effective as a discriminative stimulus in pigeons. That is, the 2 training conditions (presence and absence of morphine) guided the choice behavior of the birds by indicating on which of the 2 response keys responding would produce reinforcement during a particular training session.

The estimated median effective time interval (ET50) of 6 hr post-injection is longer than that reported for rats trained to discriminate 3 mg/kg of morphine in a discrete avoidance procedure [25] or gerbils trained to discriminate 16 or 32 mg/kg of the drug and the respective nondrug conditions in a T-shaped maze [18]. In these studies morphine appropriate responding was evident until 3 hr after the morphine injection, whereas tests carried out 6 hr post-injection predominantly resulted in responding appropriate for the nondrug condition. On the other hand, morphine-cued responding was evident still 14 hr post-injection in squirrel monkeys trained to discriminate between 3 mg/kg of morphine and saline [24]. These data might reflect species differences as

TABLE 1

SUBSTITUTION TESTS (T) WITH METHADONE AND 3 NON-OPIOID DRUGS IN PIGEONS TRAINED TO DISCRIMINATE BETWEEN SALINE (N) AND 6 MG/KG OF MORPHINE (D)

| Drug | Dose mg/kg) | Time (min) | Pigeon Number 28 | 33 | 34 | 35 | Responses on Morphine Key (%) 15 | 45 | Total |
|---|---|---|---|---|---|---|---|---|---|
| N = Saline | — | 45 | | | | | 4.2 | 3.3 | 0.2 |
| D Morphine | 6.0 | 45 | | | | | 100.0 | 100.0 | 98.9 |
| T - Methadone | 3.0 | 45 | X | | X | X | 80.0 | 93.3 | 98.3 |
| T = Methadone | 6.0 | 45 | | X | X | X | 100.0 | 100.0 | 100.0 |
| T - $\Delta^9$-THC | 0.25 | 90 | X | X | | X | 0.0 | 0.0 | 0.0 |
| T - $\Delta^9$-THC | 0.50 | 90 | X | | X* | X | 0.0 | 0.0 | 0.0 |
| T - *d*-LSD | 0.04 | 15 | X | X | | X | 0.0 | 0.0 | 0.0 |
| T - *d*-LSD | 0.08 | 15 | X | X | X | | 0.0 | 0.0 | 0.0 |
| T - P-barb. | 4.0 | 10 | | X | X | X | 0.0 | 0.0 | 0.0 |
| T - P-barb. | 8.0 | 10 | X | X | X | | 0.0 | 0.0 | 0.0 |

Three animals were used for each test dose and are identified by X. Pigeon No. 34 did not peck on either of the response keys when tested with 0.50 mg/kg of $\Delta^9$-THC. Training performances are based on a total of 48 sessions, 24 for each of the training conditions (D and N). Data are presented as the percentage pecking responses on the morphine associated key for the initial 15, 45 as well as the total number of responses emitted by the birds. Test sessions ended after 225 responses or 10 min, whichever came first.

regards the duration of the cue properties of morphine. However, all the shorter lasting effects were noted after IP injections of morphine whereas the longer lasting effects occurred after IM administrations of the drug (pigeons and squirrel monkeys). Thus the eventual species difference may primarily relate to differences in the absorption of the drug, and consequently the elimination of the drug due to differences in the mode of administration rather than true species specific differences.

The finding that the analgesically active levorphanol but not its enantiomer dextrorphan substituted for morphine in our birds agree with similar test data in rats [25,29], gerbils [18] and monkeys [24] meaning that the stereospecific requirement for narcotic action is not unique to the mammalian brain. The pharmacological profile of levorphanol resembles that of morphine although the compound is considered 3–5 times more potent than morphine [14].

Both naloxone and naltrexone antagonized morphine-key responding when given simultaneously with or 30 min after the morphine injection. When the antagonists were given 135 min prior to morphine, only naltrexone blocked the morphine-key responding in 2 pigeons; the 2 other birds responded on the morphine appropriate key. The dose-effect curves (cf. Fig. 4B) for the antagonists in blocking the training dose of morphine when given 45 min prior to testing suggest that naltrexone was 4–6 times more potent than naloxone in this regard. However, a comparison in terms of potency may be misleading because only 1 pretreatment interval was used for the dose-effect determination. It is possible that the difference in blocking efficacy of the 2 antagonists are related to the duration of their respective effects rather than potency *per se* since naloxone appears to have a shorter duration of action than its n-cyclopropyl-methyl congener naltrexone [7]. Nevertheless, the data support the second criteria (see introduction) for classifying this morphine discrimination of being of a specific narcotic nature. Drug discriminative control based upon either ethanol [29] or $\Delta^9$-THC [17] are not blocked by these antagonists, thus furthering the specificity of the present blockade.

The pigeons choose the morphine-key when tested with methadone but not when tested after treatments with 3 other non-narcotic drugs viz. $\Delta^9$-THC, d-LSD, and pentobarbital. The lack of generalization to morphine with the 3 latter drugs are not due to lack of intrinsic activity since the lower dose of each of the drugs have been shown to control choice behavior of pigeons in this procedure ([9,16] and unpublished observations). The lack of substitution effects with these non-opioid drugs further attest to the specificity of the narcotic cue in pigeons. The substitution of methadone is in agreement with previous results in rats trained to discriminate morphine or fentanyl from the nondrug condition [5, 6, 8, 25] or squirrel monkeys trained to discriminate between morphine and the no drug condition [24]. In conclusion, the discriminable effects of morphine in the pigeon are qualitatively similar to results obtained in mammals (gerbils, rats, and squirrel monkeys) required to discriminate morphine from a nondrug condition.

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